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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,274	01/12/2001	John Sinden	GJE-21D2	3086

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/760,274	**Applicant(s)** SINDEN ET AL.	
	Examiner Michael C. Wilson	**Art Unit** 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED _____ FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *25 October 2004*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): the double patenting rejection; the new matter rejections in part.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *57,58,60-62,64 and 76-86*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☒ Other: See Continuation Sheet.

MICHAEL WILSON
PRIMARY EXAMINER

Continuation of 13. Other: This advisory action is intended to be like the advisory action sent 12-21-04 containing clarification of the new matter arguments. The numerous new citations in the specification cited in the arguments made 10-25-04 are considered "new evidence" and should not be considered after final. However, it light of customer service and to expidite prosecution, the examiner clarifies the new matter arguments herein. Applicants are reminded that review of amendments and arguments after final are intended to be "cursory."

DETAILED ACTION

Applicant's arguments filed 10-25-04 have been considered in part. The new matter arguments could have been made when the amendment was filed.

Claims 1-48, 59 and 68-75 have been canceled. Claims 57, 58, 60-62, 64 and 76-86 remain pending and under consideration in the instant office action.

Claim Rejections - 35 USC § 112

Written Description

Claims 57, 58, 60-62, 64 and 76-86 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

Applicants cite Kawaguchi (Molecular and Cellular Neuroscience, 2001, 17:259-273) and Sakakibara (PNAS, 2002, 99(23)15194-1519). Sakakibara teaches musashi is a protein expressed in neural precursor cells including CNS stem cells. Kawaguchi teaches nestin is expressed in neural precursor cells. Applicants argue the human nestin-positive, musashi-positive pluripotent neural stem cells in the Declaration by Dr. Sinden were merely further characterized as expressing musashi 1, in addition to nestin. Applicants conclude the experimental results in the Declaration by Dr. Sinden should not be disqualified as evidence of written description. Applicants' arguments are not persuasive. The art does not teach nestin and musashi were expressed in the

same populations of pluripotent neural stem cells. Sakakibara taught musashi was specific for the development of aqueductal ependymal cells and that musashi expression was highly restricted to cell populations in the ependyma lining the aqueduct. (pg 15198, col. 2, Discussion). Kawaguchi simply taught nestin was generic to neural precursor cells. The nestin-positive, musashi-positive, human, pluripotent, neural precursor cells described in the Declaration by Dr. Sinden as having the desired function *in vivo* have a narrower scope than nestin-positive, human, pluripotent, neural precursor cells described in the specification as originally filed. As such, applicants did not adequately describe that which was essential to obtain human neural precursor cells having the desired function, i.e. nestin-positive neural precursor cells expressing musashi. The experimental results in the Declaration by Dr. Sinden remain unpersuasive because the cells used in the experiment were of a narrower scope than those described in the specification as originally filed and because musashi expression may be essential to obtain nestin-positive neural precursor cells with the desired function in humans.

Please argue written description and enablement rejections separately.

Please include a separate heading for the written description arguments.

New Matter

The phrase "a disorder associated with damage to, or loss of, brain cells in a mammal" in claims 57, 81 and 85 remains new matter. Applicants point to pg 1, line 19-25 and pg 5, lines 15-22. Pg 1, lines 19-25, states: "pluripotent neuroepithelial cells

appear to respond to signals from the damaged or diseased brain by taking up a phenotype that is able to replace or compensate for functional deficits to which the damage or disease otherwise leads." Pg 5, lines 15-22, states "The phenotype of the differentiated cells may be the same as the phenotype of the damaged or lost cells, however, the differentiated cells may be of a different phenotype, or of a number of phenotypes. In any case, the cells take up a phenotype that is capable of functionally integrating and compensating for the damaged or lost cells." applicants' argument is not persuasive. The citations do not contemplate the scope of "disorders associated with damage to, or loss of, brain cells." The scope of treating a disorder "associated with" damage to, or loss of, brain cells is different than treating a diseased brain having damage to, or loss of, brain cells as contemplated in the specification. More disorders may be "associated with" brain damage or loss of brain cells than just those in which brain damage or brain cell loss occurs. For example, alcoholism is "associated with" brain cell loss but is not contemplated as one of the disorders on pg 1, lines 19-25, or pg 5, lines 15-22. The claims should be limited to treating damage to, or loss of, brain cells as on pg 5, lines 15-22.

The rejection regarding the phrase "wherein said cells are immortal prior to said transplanting and differentiate after said transplanting" in claim 57 has been withdrawn. Applicants point to pg 5, lines 10-15, and lines 32-36; pg 6, lines 1-10 and 16-25. Pg 5, lines 10-15, states: "We have found that when conditionally immortal pluripotent neuroepithelial cells are implanted into a damaged brain the cells differentiate into the correct form of cell required to repair the damage and the differentiated cells are able to

form the appropriate connections required to improve function." Pg 6, lines 6-10, states: "If the conditions under which the cells are maintained are switched to nonpermissive conditions, the development of the cells is allowed to continue. If the correct conditions are provided the cells will continue to develop and will differentiate." Pg 6, lines 16-25, states: "Conditionally immortal cells have the advantages of immortal cells in that they are "frozen'" in the desired stage of development, are easily maintained and multiply well when under permissive conditions but they nay be used in transplants as long as the environment into which they are transplanted has nonpermissive conditions. In the case of the cells of the present invention the gene used to confer conditional immortality should be chosen so that the conditions present in the brain will correspond to nonpermissive conditions." Applicants' arguments are persuasive.

The rejection regarding the phrase "wherein said transplanting improves brain function of said mammal" in claims 57 and 81 has been withdrawn. Applicants point to pg 8, lines 1-5, which states: "in response to the local microenvironment, into the necessary phenotype or phenotypes to improve or restore function." It is readily apparent that the phrase improve or restore function relates to brain function as claimed.

The phrase "a disorder associated with damage to, or loss of, brain cells in the hippocampus of said mammal" in claim 58 remains new matter. Applicants cite pg 5, lines 15-22; pg 13, lines 2-4; Examples 5-9 on pg 22-29. Pg 5, lines 15-22, states: "The phenotype of the differentiated cells may be the same as the phenotype of the damaged or lost cells, however, the differentiated cells may be of a different phenotype, or of a

number of phenotypes. In any case, the cells take up a phenotype that is capable of functionally integrating and compensating for the damaged or lost cells." Pg 13, lines 2-4, states "Transplantation into any is envisaged with consequent improvement in function." Applicants' arguments are not persuasive. The citations do not contemplate the scope of "disorders associated with damage to, or loss of, brain cells in the hippocampus." The scope of treating a disorder "associated with" damage to, or loss of, brain cells is different than treating a diseased brain having damage to, or loss of, brain cells as contemplated in the specification. More disorders may be "associated with" brain damage or loss of brain cells than just those in which brain damage or brain cell loss occurs. For example, alcoholism may be "associated with" brain cell loss of the hippocampus but is not contemplated as one of the disorders contemplated in the specification as originally filed. Examples 22-29 do not contemplate the breadth of disorders "associated with" brain damage as newly claimed. The claims should be limited to treating damage to, or loss of, brain cells in the hippocampus as on pg 5, lines 15-22, taken with pg 13, lines 2-4.

The rejection regarding the phrase "wherein said transplanting improves cognitive function of said mammal" in claims 57 and 81 has been withdrawn. Applicants cite pg 8, lines 15-27; pg 9, lines 29-35; and pg 10, lines 1-9. Pg 8, lines 15-27, states: "After treatment the progress of the patient maybe monitored using behavioral and/or psychological tests and/or, if desired, tests which monitor brain activity in selected areas of the brain. For example, tests for cognitive function may be performed before and after transplantation. Preferably, treatment will substantially correct a behavioral and/or

psychological deficit. However, that may not always be possible. Treatment according to the present invention and with the cells, medicaments and pharmaceutical preparations of the invention, may lead to improvement in function without complete correction. Such improvement will be worthwhile and of value." Pg 9, lines 29-35, states: "below. The lesion-and-behaviour model in which we have demonstrated that cloned cell lines are able to restore function in the damaged brain is one that we have previously studied intensively using fetal conspecific transplants (see Sinden et al., 1995). It utilizes rats in which the technique for four-vessel occlusion (4 VO),...." Pg 10, lines 1-9, state: "circumscribed and specific damage to the CAI pyramidal cells of the dorsal hippocampus, along with a cognitive deficit manifest as difficulty in locating a submerged and invisible platform in a swimming pool. This lesion and behaviour model provides a model of cognitive dysfunction occurring as a consequence of a common form of brain damage, i.e., transient loss of blood supply to the brain, for example, as may occur during cardiac arrest." Applicants' arguments are persuasive.

The rejection regarding treating humans as in claims 82 and 86 has been withdrawn. Applicants cite pg 2, lines 14-17, which states: "The treatment may be carried out on any mammal but the present invention is especially concerned with the cells, and with human cells and cell lines." Applicants' argument is persuasive.

The rejection regarding the specification as a whole not support using any nestin-positive, neuroepithelial cells has been withdrawn. Applicants cite pg 13, lines 5-7: pg 12, lines 33-36; pg 13, lines 1-4; Examples 6-8; and pg 3, lines 1-14 of the specification. Pg 13, lines 5-7, state: "The part of the fetal brain from which the neuroepithelial cells

are taken and the precise time (stage and development) may vary." Pg 12, lines 33, through pg 13, line 4, states: "In the experiments on rats which are described in Examples 6, 7 and 8 below conditionally immortal pluripotent cells have been used to repair a very specific type of damage. The uses of cells according to the invention are not limited to repair of that particular type of damage. Transplantation into any area of the brain is envisaged with consequent improvement in function." Applicants' arguments are persuasive.

The rejection regarding improving any "brain function" by adding neuroepithelial cells has been withdrawn in view of applicants' arguments (pg 10).

Please include a separate heading for the new matter arguments.

Enablement

Claims 57, 58, 60-62 and 76-86 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a cognitive deficit in a rat caused by a hippocampal lesion comprising administering mouse, hippocampal, nestin-positive, pluripotent, neuroepithelial cells comprising a vector encoding tsA58 operably linked to the H-2Kb promoter to the hippocampus of the rat such that the cognitive deficit is treated, does not reasonably provide enablement for i) using any pluripotent, nestin-positive neuroepithelial cells to treat any disorder associated with damage to, or loss of, any brain cells, ii) treating damaged brain cells by implanting genetically modified cells anywhere within the brain, iii) using nestin-positive, pluripotent, neuroepithelial cells to treat a disorder associated with damage to, or loss

of, brain cells in a human, or iv) using any "conditionally immortal" cells as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Applicants cite Kawaguchi (Molecular and Cellular Neuroscience, 2001, 17:259-273) and Sakakibara (PNAS, 2002, 99(23)15194-1519). Sakakibara teaches musashi is a protein expressed in neural precursor cells including CNS stem cells. Kawaguchi teaches nestin is expressed in neural precursor cells. Applicants argue the human nestin-positive, musashi-positive pluripotent neural stem cells in the Declaration by Dr. Sinden were merely further characterized as expressing musashi 1, in addition to nestin. Applicants conclude the experimental results in the Declaration by Dr. Sinden should not be disqualified as evidence of enablement. Applicants' arguments are not persuasive. The art does not teach nestin and musashi were expressed in the same populations of pluripotent neural stem cells. Sakakibara taught musashi was specific for the development of aqueductal ependymal cells and that musashi expression was highly restricted to cell populations in the ependyma lining the aqueduct. (pg 15198, col. 2, Discussion). Kawaguchi simply taught nestin was generic to neural precursor cells. The nestin-positive, musashi-positive, human, pluripotent, neural precursor cells described in the Declaration by Dr. Sinden as having the desired function *in vivo* have a narrower scope than nestin-positive, human, pluripotent, neural precursor cells described in the specification as originally filed. As such, applicants did not adequately teach those of skill that which was essential to obtain human neural precursor cells

having the desired function, i.e. musashi expression. The experimental results in the Declaration by Dr. Sinden remain unpersuasive because the cells used in the experiment were of a narrower scope than those described in the specification as originally filed and because musashi expression may be essential to obtain nestin-positive neural precursor cells with the desired function in humans.

Double Patenting

The rejection of claims 57, 58, 60-62 and 76-86 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application Nos. 10/342692 and 10/376119 has been withdrawn in view of the terminal disclaimers filed 10-25-04.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER